PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 4 :
C07D 487/04, A61K 31/435
C07D 401/04 // (C07D 487:04
C07D 231:00, 231:00)
(C07D 487/04, 237:00, 231:00)

A1

(11) International Publication Number: WO 89/10924

(43) International Publication Date: 16 November 1989 (16.11.89)

(21) International Application Number: PCT/GB89/00517

(22) International Filing Date: 12 May 1989 (12.05.89)

(30) Priority data:
8811299.0 12 May 1988 (12.05.88) GB

(71) Applicant *(for all designated States except US)*: NATIONAL RESEARCH DEVELOPMENT CORPORATION [GB/GB]; 101 Newington Causeway, London SE1 6BU (GB).

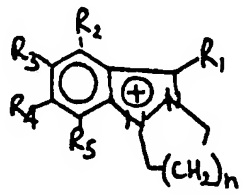
(72) Inventors; and
(75) Inventors/Applicants *(for US only)* : GRAYSHAN, Roger [GB/GB]; 70 Redford Avenue, Colinton, Edinburgh EH13 0BW (GB). FRENCH, Andrew, McKinnon [GB/GB]; 6 Salamanca Crescent, Greenlan Mains, Penicuik EH26 0LN (GB). AL-KHAMMEES, Hamad [SA/SA]; Department of Pharmaceutical Chemistry, College of Pharmacy, King Saud University, P.O. Box 2457, Riyadh 11451 (SA). DE BOOS, Gareth, Andrew [GB/GB]; 16 Viewforth Square, Edinburgh EH10 4LW (GB).

(74) Agent: CARDNELL, Peter, Harry, Morley; Patent Department, National Research Development Corporation, 101 Newington Causeway, London SE1 6BU (GB).

(81) Designated States: AT (European patent), BE (European patent), CH (European patent), DE (European patent), FR (European patent), GB (European patent), IT (European patent), JP, LU (European patent), NL (European patent), SE (European patent), US.

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: INDAZOLE DERIVATIVES



(II)

(57) Abstract

A compound of formula (II), or a pharmaceutically acceptable acid additon salt thereof in which formula R_1 represents a six membered heterocyclic ring A comprising one nitrogen atom and bound to the indazole ring system by carbon, the ring A being optionally substituted by one or more C_1-C_6 alkyl groups; R_2 represents hydrogen, hydroxy, C_1-C_6 alkyl or C_1-C_6 alkoxy; R_3 represents hydrogen, hydroxy, halogen, a C_1-C_6 alkyl or alkoxy group, or a group of formula $-NO_2$, -CN, $-CONH_2$ or -CONHR (R representing a C_1-C_3 alkyl group); R_4, which may differ from R_3, represents: hydrogen, hydroxy, halogen, a C_1-C_6 alkyl or alkoxy group, or a group of formula $-NO_2$, -CN, $-CONH_2$, or -CONHR (R representing a C_1-C_3 alkyl group); R_5 represents hydrogen or halogen; X^- represents an anionic moiety the nature of which is such that the compound of formula (II) is pharmaceutically acceptable and n is 1 or 2.

Ref B12

FOR THE PURPOSES OF INFORMATION ONLY

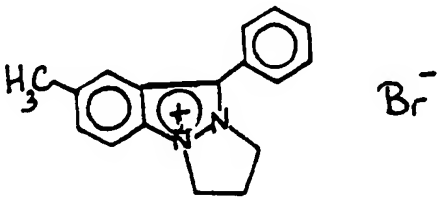
Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	FI	Finland	ML	Mali
AU	Australia	FR	France	MR	Mauritania
BB	Barbados	GA	Gabon	MW	Malawi
BE	Belgium	GB	United Kingdom	NL	Netherlands
BF	Burkina Fasso	HU	Hungary	NO	Norway
BG	Bulgaria	IT	Italy	RO	Romania
BJ	Benin	JP	Japan	SD	Sudan
BR	Brazil	KP	Democratic People's Republic of Korea	SE	Sweden
CF	Central African Republic			SN	Senegal
CG	Congo	KR	Republic of Korea	SU	Soviet Union
CH	Switzerland	LI	Liechtenstein	TD	Chad
CM	Cameroon	LK	Sri Lanka	TG	Togo
DE	Germany, Federal Republic of	LU	Luxembourg	US	United States of America
DK	Denmark	MC	Monaco		
ES	Spain	MG	Madagascar		

INDAZOLE DERIVATIVES

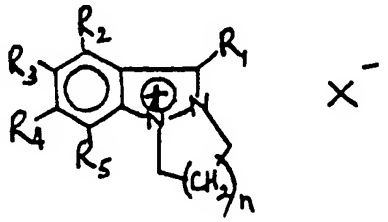
This invention relates to indazole derivatives, and in particular to pyrazolo - and pyridazinoindazole derivatives, processes for their preparation and pharmaceutical compositions containing them.

In intensive efforts to find a bronchodilating agent for the treatment of asthma which is more satisfactory than the xanthine derivatives and beta-adrenoreceptor stimulants used at present, various indazole derivatives have been tested. The compound I, (2,3-dihydro-7-methyl-9-phenyl-1H-pyrazolo(1,2-a)indazolium bromide) is said to be particularly promising

I 

It has now been found that certain indazole derivatives have a bronchodilating activity which exceeds that of the demethylanalogue of compound I and, it is envisaged, will exceed that of Compound I per se.

Accordingly, the present invention comprises a compound of formula II or a pharmaceutically acceptable acid addition salt thereof:

II 

in which formula R_1 represents a six membered heterocyclic ring A comprising one nitrogen atom and bound to the indazole ring system by carbon, the ring A being optionally substituted by one or more C_1-C_6 alkyl groups;

R_2 represent hydrogen, hydroxy, C_1-C_6 alkyl or C_1-C_6 alkoxy,

R_3 represents hydrogen, hydroxy, halogen, a C_1-C_6 alkyl or alkoxy group, or a group of formula $-NO_2$, -CN,$-CONH_2$, or -CONHR (R representing a C_1-C_3 alkyl group);

R_4, which may differ from R_3, represents: hydrogen, hydroxy, halogen, a C_1-C_6 alkyl or alkoxy group, or a group of formula $-NO_2$, -CN,$-CONH_2$, or -CONHR (R representing a C_1-C_3 alkyl group);

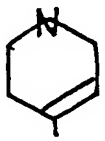
R_5 represents hydrogen or halogen,

X^- represents an anionic moiety the nature of which is such that the compound of formula II is pharmaceutically acceptable and

n is 1 or 2.

In the compound II of the present invention, the nitrogen atom of ring A is preferably spaced from the carbon of the indazole ring system on which ring A is carried by three carbon atoms, that is the nitrogen of ring A is remotely located from the point of connection to the indazole ring system. Ring A may be aromatic, saturated or monounsaturated, in the latter case suitably adjacent the bond joining ring A to the indazole ring system as in the following case:

R_1:



Compounds of the latter type are of particular interest. The nitrogen may be unsubstituted or carry a C_1-C_6 alkyl group, an acyl group of formula -COR' in which R' represents a C_1-C_6 alkyl group or a sulphonate group of formula $-SO_2R''$, in which R''

represents a C_1-C_3 alkyl or aryl group.

The substituent R_2 preferably represents hydrogen, hydroxy, C_1-C_3 alkyl or alkoxy, X^- preferably represents halide and especially bromide, the substituent R_3: hydrogen, hydroxy, C_1- C_3 alkyl or alkoxy or halogen, the substituent R_4: hydrogen, hydroxy, C_1-C_3 alkyl or alkoxy or halogen and n is preferably one.

Typically X^- is an anionic moiety of one of the following acids: hydrochloric, hydrobromic, sulphuric, nitric, isethionic, phosphoric, maleic, salicyclic, p-toluenesulphonic, tartaric, citric, lactobionic, formic, malonic, pantothenic, succinic, naphthalene-2-sulphonic, benzenesulphonic, methanesulphonic, ethanesulphonic, sulphonic, carbonic, acetic and benzoic. When compound II is present in the form of an acid addition salt (in which case the compound is a double salt), the additional anion present is generally derived from one of the acids hereinbefore described, an acid halide e.g. hydrobromide or hydrochloride being particularly preferred.

In compounds of particular interest both R_4 and R_5 represent hydrogen R_2 represent hydrogen or C_1-C_6 alkoxy and R_3 represents hydrogen, halogen, a C_1-C_3 alkyl group or a group of formula $-NO_2$, -CN, $-CONH_2$, or -CONHR (R representing a C_1-C_3 alkyl group).

The following compounds (and acid salts thereof e.g. hydrochlorides) are of particular interest:

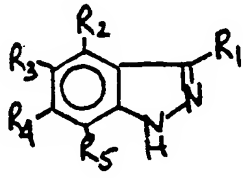
(i) 2,3-Dihydro-9(1-methyl-1,2,5,6 tetrahydro-4-pyridyl)-1-4-pyrazolo(1,2-a)indazolium bromide; (ii) 2,3-dihydro-9(1-methyl)-4-pyridyl)-1-4-pyrazolo-(1,2a)-indazolium bromide; (iii) 2,3-dihydro-9(1-methyl)-4-piperidyl)-1-4-pyrazolo-(1,2a)-indazolium bromide; (iv) 7-methyl-2,3-dihydro-9(1-methyl-1,2,5,6 tetrahydropyridyl)-1-4 pyrazolo(1,2-a)- indazolium bromide; (v) 7-methyl-2,3-dihydro-9(1- ethyl-1,2,5,6 tetrahydropyridyl)-1-4-pyrazolo(1,2-a) indazolium bromide. In the compounds (iv) and (v) R_3 of formula II represents, of course, methyl.

The present invention further includes within a further aspect a compound of formula II or a pharmaceutically acceptable acid addition salt thereof for use in therapy and in particular

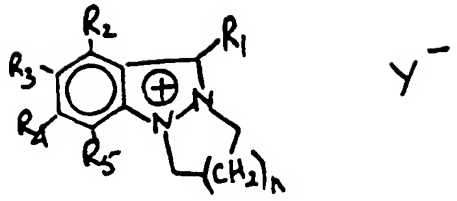
for use in the treatment of prophylaxis of asthma. In a yet further aspect of the invention an asthmatic subject is treated with a compound of formula II or a pharmaceutically acceptable acid addition salt thereof in an amount effective to dilate the bronchi. The compound of formula II or a pharmaceutically acceptable acid addition salt thereof is generally administered in the form of a composition comprising a pharmaceutically acceptable diluent or carrier, typically orally, by injection or inhalation and in unit dosage form. Although it is envisaged that precise recommended doses will be established by trial, LD_{50} values indicate that typically a dose of 50-100mg will be administered to human patients at least once and usually twice daily.

Compounds II according to the present invention may be prepared from the corresponding indazole or acid addition salt thereof.

In accordance with a further aspect of the present invention, a process for the production of a compound II or a pharmaceutically acceptable acid addition salt thereof comprises treating an indazole of formula III or an acid addition salt thereof,

III 

with a substituted alkane of formula $Y-(CH_2)_{n+2}-Z$ wherein Y and Z which may be identical or different, represent moieties capable of existence as anions in the presence of a reducing agent such as a hydride e.g. an alkali metal hydride whereby a compound of formula IV is produced the counterion Y^- of which is, when necessary, subsequently replaced by a counterion X^-.

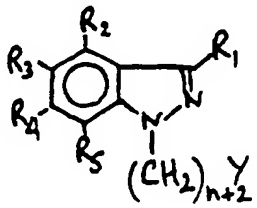
IV 

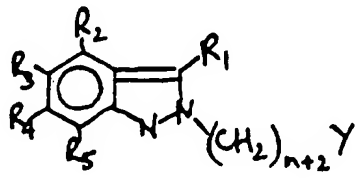
Treatment of compound III is generally conducted in a solvent such as dimethyl formamide, the temperature generally being maintained at least initially below 0°C. Subsequent heating to a temperature between ambient and 100°C, typically 40-50°C. may be required.

In a preferred procedure, after treatment of the indazole (or addition salt) with reducing agent, the reaction mixture is rendered acidic prior to cyclization.

In general Y & Z both represent chlorine or bromine and when a compound II is required in which X^- is other than chloride or bromide the compound IV is treated with a source of X^-, such as an ion exchange resin, so that Y^- is replaced by X^-.

In some cases it is possible to isolate an intermediate which is of formula V, or VI or is an acid addition salt thereof. Such an intermediate or a mixture of such intermediates, on application of heat, preferably when in acid solution yields the compound II or an addition salt thereof

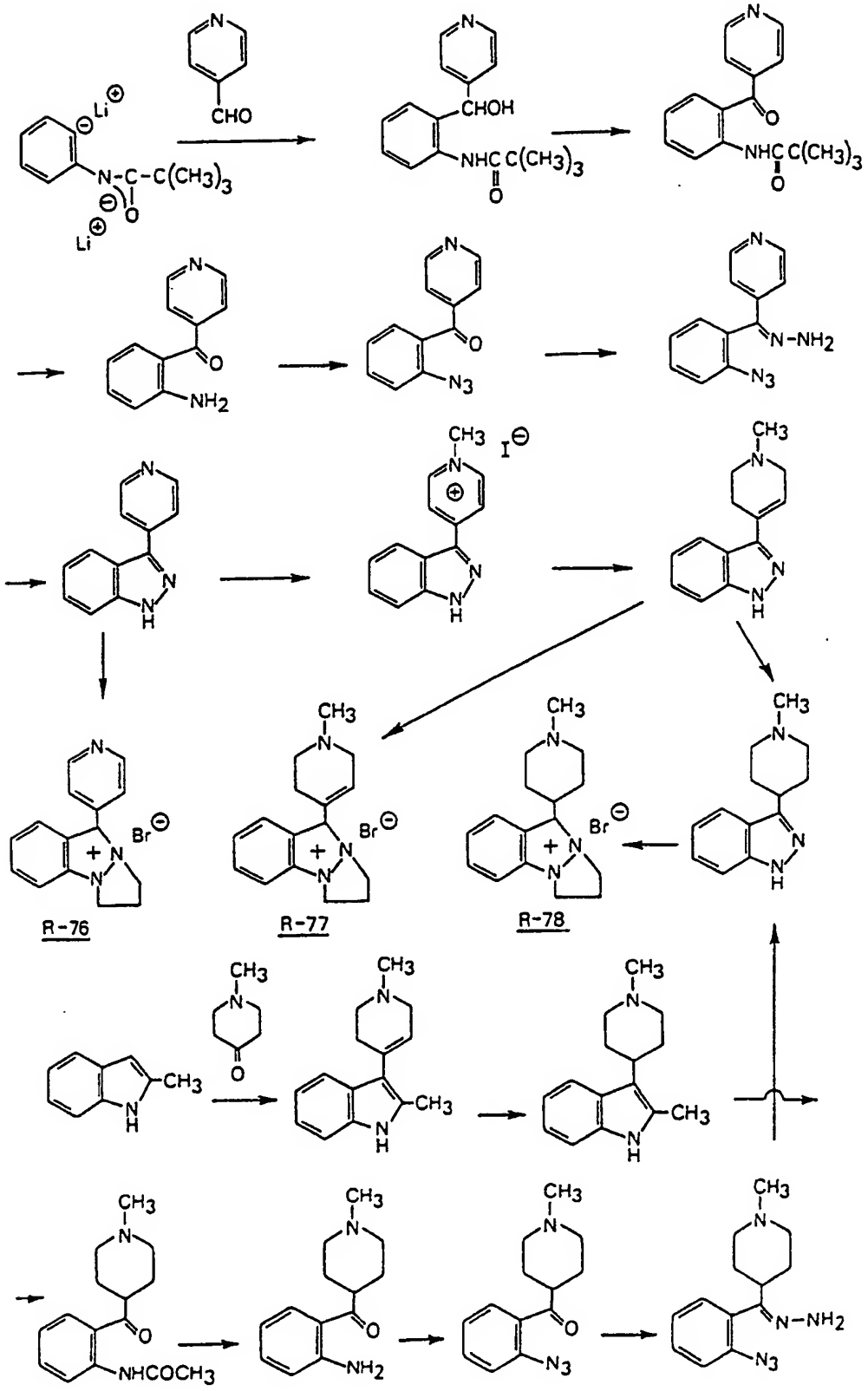
V 

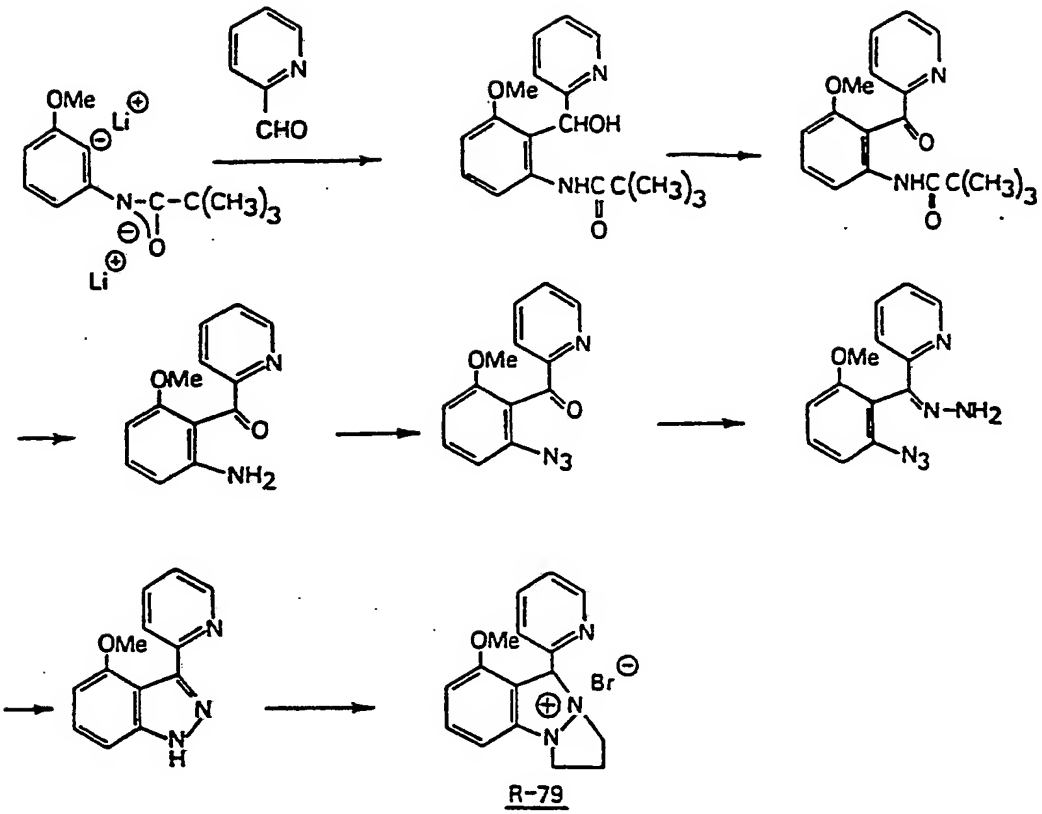
VI 

The solution is preferably dilute and the solvent inert.

Compounds of formula II may be generated by following various routes of which those now shown in Sheets I, IA and II below are illustrative. It will be appreciated that the routes outlined in these Sheets overlap considerably.

SHEET I





R-79

Reagents

i) 4-Pyridyl-carboxaldehyde/tetrahydrofuran.

ii) Jones' reagent/propanone.

iii) 6M Hydrochloric acid aq./ethanol.

iv) Boron trichloride/dichloromethane/4-cyano-pyridine/1,1,2,2-tetrachloroethane; aluminium trichloride; hydrochloric acid aq.

v) 10% Palladium-carbon/ethanol/hydrazine hydrate.

vi)a) 10M Hydrochloric acid aq.; sodium nitrite aq.; sodium azide aq.; sodium bicarbonate aq.; hydrazine hydrate/ethanol/ethanoic acid.

b) 10M Hydrochloric acid aq.; sodium nitrite aq.; sodium bisulphite aq.

or c) 10M Hydrochloric acid aq.; sodium nitrite aq.; tin dichloride aq.

vii) 1-Methyl-4-piperidone/2N phosphoric acid aq./ethanoic acid.

viii) Iodomethane/ethyl ethanoate.

ix) Borane-dimethyl sulphide/tetrahydrofuran; trimethyl amine N-oxide dihydrate.

x) Sodium periodate/methanol aq.

xi) Sodium borohydride/methanol.

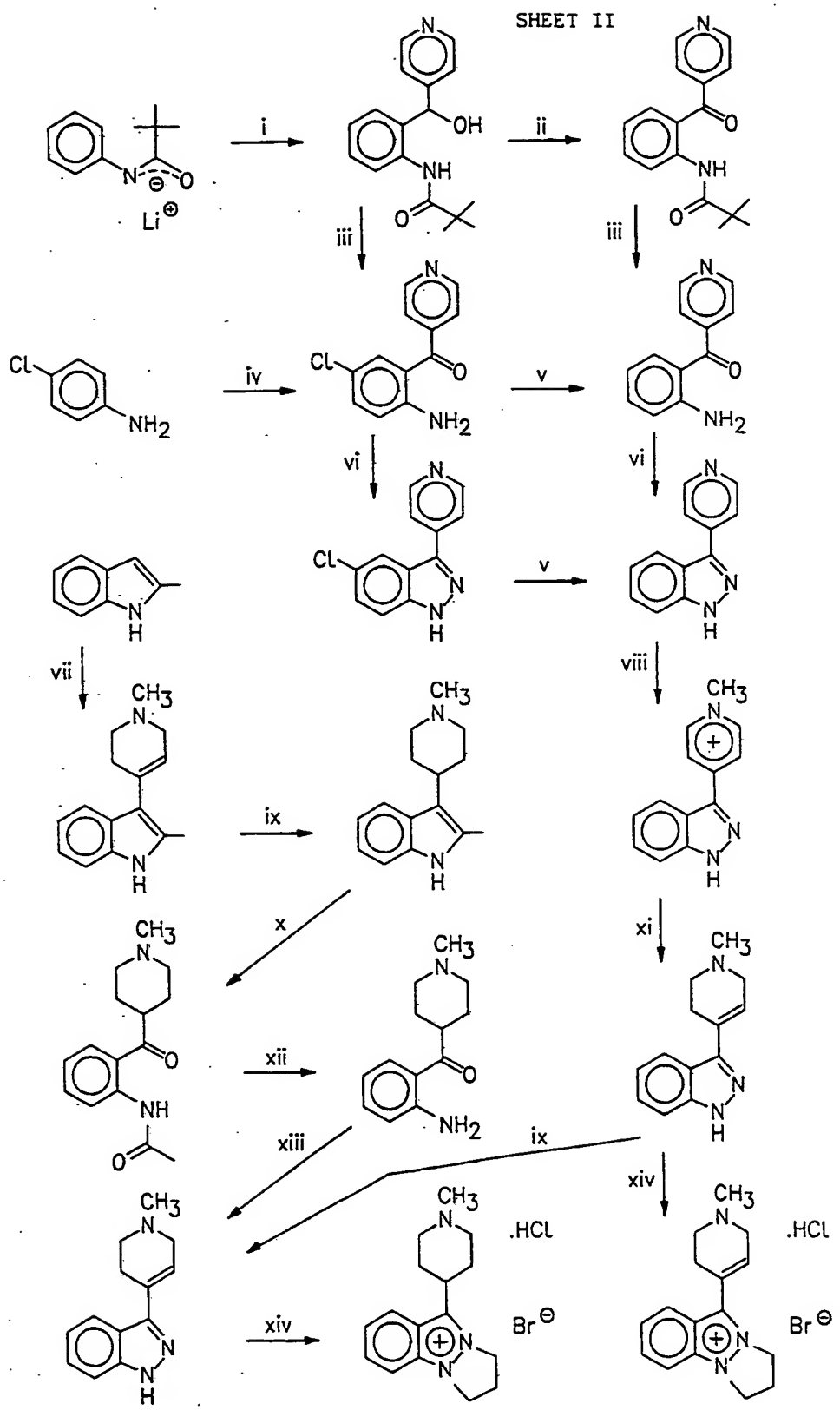
xii) 5M Hydrochloric acid aq./ethanol.

xiii)a) 10M Hydrochloric acid aq.; sodium nitrite aq.; sodium azide aq.; sodium bicarbonate aq.; hydraziue hydrate/ethanol/ethanoic acid.

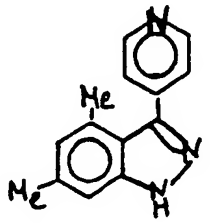
or b) 10M Hydrochloric acid aq.; sodium nitrite aq.; tin dichloride aq.

xiv) Sodium hydride/dimethyl methanamide; 1,3-dibromo-propane; 0.3MM hydrochloric acid aq./methanol; butanol/hcat.

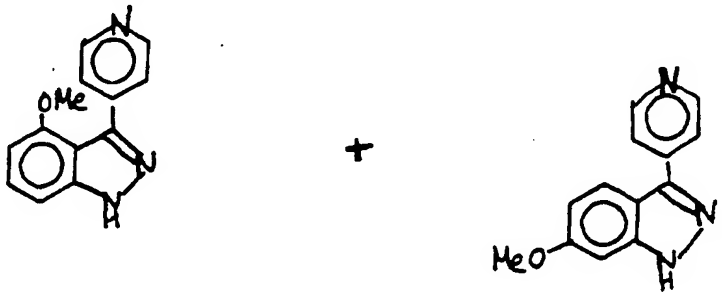
SHEET II


i
ii
iii
iii
iv
v
vi
vi
v
vii
viii
ix
x
xi
xii
xiii
ix
xiv
xiv
.HCl
.HCl
Br⊖
Br⊖
Li⊕
Cl
NH2
OH
NH
O
N
CH3
H

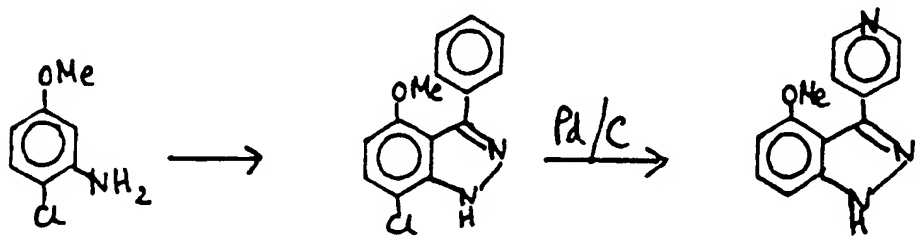
When an anilino precursor of an intermediate of formula III has a plane of symmetry (which intersects the benzene nucleus as right angles) the bicyclic product therefrom generally consists of only one isomer. For example the compound 3,5-dimethylaniline is readily convertible into the following compound:-



When however no such plane of symmetry exists, as in 2-methoxyaniline, a mixture of the following isomers is produced:



It has been found that a halogen substituent, suitably ortho to the $-NH_2$ group may be used to block the formation of an unwanted isomer from an anilino starting material and can be subsequently removed, if desired. This route is illustrated by the following conversion.



The present invention is illustrated by the following examples:-

Example 1:

2,3-Dihydro-9(1-Methyl-1,2,5,6-Tetrahydro-4-Pyridyl) 1-4-Pyrazolo-(1,2-a)-Indazolium Bromide (Compound R77).

A. (±) (2-(2,2-Dimethylpropanamido)phenyl-pyrid-4-yl-methanol.

Butyl lithium (32.0g; 0.5mol) in hexane was added dropwise to a solution of 2,2-dimethylpropanamidobenzene (45.0g; 0.25mol) in dry tetrahydrofuran (1l) at 0°C under nitrogen and then, the mixture was stirred at this temperature for two hours. A solution of 4-pyridine-carboxaldehyde (26.7g) in tetrahydrofuran (300ml) was added dropwise. Following this addition, the reaction mixture was stirred for one hour at 0°C and then at ambient temperature overnight. After that, the reaction mixture was quenched with ice/water and the tetrahydrofuran was evaporated to a minimum volume. The aqueous solution was extracted with diethyl ether which was dried, filtered and the solvent evaporated to give a brown oil. Silica chromatography using petroleum ether: diethyl ether as eluting solvent gave the product (41.8g; 58%) as a white solid.

m.p.	154-156°C.
i.r.	3597 (OH), 3340 (NH) and (C=O) 1664cm^{-1}
^{1}H n.m.r.	9.30 (H, b, NH); 8.41-8.09 (2H, m, aromatic); 7.51-701 (6H, m, aromatic); 5.90-5.75 (1H, b, (CHOH); 1.04 (9H, s, $(CH_3)_3$) p.p.m.

B. (2-(2,2-Dimethylpropamido)phenyl)-4-pyridyl-methanone.

Jones' reagent was added to a solution of 2-(2,2-dimethyl-propanamido)phenyl-pyrid-4-yl-methanol (38.0g; 0.3lmol) in propanone (400ml) at 0°C until the solution was deep orange. The reaction mixture was allowed to stir for thirty minutes, then sulphur dioxide saturated propanone was added to destroy any

excess of the reagent. Water was added and the product extracted with ethyl ethanoate. The extract was dried, filtered and the solvent evaporated to give a yellow oil (35.g; 95%). Purification by silica chromatography of a sample gave a small amount of the pure product as a pale yellow oil.

i.r. 3310 (NH), 1683 (NHCO). and (C=O) 1635cm^{-1}

n.m.r. 8.90-863 (2H, m, aromatic); 7.79-6.95 (6H, m, aromatic); 1.36 (9H, s, $(CH_3)_3$) p.p.m.

C. 2-Aminophenyl-4-pyridyl-methanone.

(From (2-(2,2-dimethylpropanamido)-phenyl)-4-pyridyl-methanone). To a stirred solution of (2-(2,2-dimethylpropanamido)-phenyl)-4-pyridyl-methanone (32.0g; 0.11mol) in ethanol (400ml), 10M aqueous hydrochloric acid (150ml) and water (100ml) were added. The reaction mixture was heated under refluc for twenty hours, then after cooling, it was poured into water and basified with 2M aqueous sodium hydroxide. The mixture was extracted with diethyl ether. After drying, filtering and evaporation of the solvent, a yellow crystalline solid was obtained (19.5g; 87%).

m.p. 162-164°C.

i.r. 3500, 3360 (NH_2) and (C=O) 1635cm^{-1}

^{1}H n.m.r. 8.95-8.55 (2H, b, NH_2); 7.50-6.21 (8H, m, aromatic) p.p.m.

^{13}C n.m.r. (CD_3CO_2D) 106.5 (s); 153.4 (s); 151.4 (s); 147.9 (d); 136.5 (d); 134.9 (d); 124.6 (d); 118.3 (d); 116 (s); 116.3 (d) p.p.m.

D. 2-Azidophenyl-4-pyridyl-methanone.

10M Aqueous hydrochloric acid (100ml) was added dropwise to a stirred solution of 2-aminophenyl-4-pyridyl-methanone (18.0g; 91 mmol) in propanone (40ml) at 0°C. After the addition of the acid, the propanone was removed under reduced pressure and the solution cooled again to 0°C. A solution of sodium nitrite

(7.5g; 109 mmol) in water (30ml) was then added to the reaction mixture followed after 30 minutes by the addition of a solution of sodium azide (14.1g; 218 mmol) in water (40ml). The mixture was then stirred for a further 30 minutes, neutralised with 10% aqueous sodium bicarbonate solution and extracted with ethyl ethanoate. Solvent evaporation of the dried and filtered extract gave the crude product (16.5g; 81%). Purification by silica chromatography of a sample gave a small amount of the pure product as a yellow oil.

i.r. 2109 (N_3) and (C=O) 1675cm^{-1}

^{1}H n.m.r. 8.80-8.31 (2H, m, aromatic); 7.41-6.92 (6g, m, aromatic) p.p.m.

E. 3-(4-Pyridyl)-indazole.

(From 2-azidophenyl-4-pyridyl-methanone.) 2-Azidophenyl-4-pyridyl-methanone (15.0g; 67 mmol) in absolute ethanol (400ml) was refluxed for seven hours, with hydrazine hydrate (65ml; 1.5 mol) and glacial ethanoic acid (5 ml). The reaction mixture was cooled, neutralised with glacial ethanoic acid, water was added, and then it was extracted with ethyl ethanoate. The extract was dried, filtered and the solvent evaporated to give a white solid (7.1g; 55%) which was recrystallised from diethyl ether to give the pure product in the form of white needles.

m.p. 187-189°C

i.r. (NH) 3460cm^{-1}

^{1}H n.m.r. 8.80-8.31 (H, b, NH); 8.10-6.91 (8H, m, aromatic) p.p.m.

F. 1-Methyl-4-(indazol-3-yl)-pyridinium iodide

Iodomethane (4.6g; 33 mmol) was added to a well stirred solution of 3-(4-pyridyl)-indazole (6.0g; 30.7 mmol) in ethyl ethanoate (100ml). The reaction mixture was heated under reflux for four hours. The precipitate obtained was separated and the solvent was evaporated to a smaller volume from which further

product was filtered off to give a total yield of the product (8.9g; 86%) as a brown solid.

m.p. 230°C (decomp.).

^{1}H n.m.r. 8.85(2H, complex d, pyridyl); 8.68(2H, complex d, pyridyl); 8.28 (1H, d, C(5)-H); 7.43(1H, dd, C(6)-H); 7.55 (1H, dd, C(7)-H); 7,72 (1H, d, C(8)-H); 4.40(3H, s, NCH_3).

G. 3-(1-Methyl-1,2,5,6-tetrahydro-pyrid-4yl)-indazole.

Sodium borohydride (0.45g) was added in small portions to a cooled and stirred solution of 1-methyl-4-(indazol-3-yl)-pyridinium iodide (2.1g; 6.2 mmol) in dry methanol (50ml). The reaction mixture was stirred at 0°C for one hour, then the solvent was evaporated. The residue was extracted into trichloro-methane and purified by silica chromatography to give the pure product as a white solid (1.2g; 92%).

m.p. 158-159°C.

i.r. 3462 (NH) and (N-CH_3) 2780cm^{-1}

^{1}H n.m.r. 8.01-7.75 (1H, m, aromatic); 7.45-6.95 (3H, m, aromatic); 6.60-6.35 (1H, m, CH=C); 3.41-2.55 (6H, m, CH_2); 2.48 (3H, s, CH>) p.p.m.

^{13}C n.m.r. (CD_3OD): 145.6 (s); 143.1 (s); 130.9 (s); 127.5 (d); 124.1 (d); 122.2 (d); 122.0 (d); 121.3 (s); 111.3 (d); 55.2 (t); 52.8 (t); 45.5 (q); 28.0 (t) p.p.m.

H. 2,3-Dihydro-9-(1-methyl-1,2,5,6-tetrahydropyrid-4-yl)-1H-pyrazolo-(1,2-a)-indazolium bromide hydrochloride. (R.77 acid salt)

Sodium hydride as a 60% dispersion in oil (210mg) was added to dimethyl methanamide (25ml) at 0°C with stirring under a nitrogen atmosphere. 3-(1-Methyl-1,2,5,6-tetrahydropyrid-4-yl)-indazole (1.10g; 5.16 mmol) dissolved in dimethyl methanamide (25ml) was added dropwise to the slurry over ten minutes. The reaction mixture was stirred at ambient temperature for thirty minutes before being cooled to 0°C. This mixture was added via a

cannula needle dropwise over ten minutes to a solution of 1,3-dibromopropane (1.04g) in dimethyl methanamide (15ml). After thirty minutes, the reaction mixture was allowed to reach ambient temperature and was stirred for three hours. The mixture was quenched on ice water and extracted with trichloromethane. After drying over potassium carbonate and magnesium sulphate and filtering, the solvent was removed at ambient or lower temperature under partial vacuum. Silica chromatography provided the intermediate compound as the least polar product. This intermediate pale yellow solid (385mg) was taken up in butanol (40ml) and 0.33M aqueous hydrochloric acid (3.5ml) was added. After refluxing for two hours, the solvent was removed by evaporation. The white solid so obtained was washed with a little trichloromethane and ethyl ethanoate, and then dried, to give 2,3-dihydro-9-(1-methyl-1,2,5,6-tetrahydro-pyrid-4-yl)-1H-pyrazolo-(1 ,2-a)-indazolium bromide hydrochloride (340mg; 18%).

m.p.	>200°C
i.r.	3400 (NH) and 2740 (N-CH_3)cm^{-1}
m.a.	
m.s.	
^{1}H n.m.r.	8.20-7.15(4H, m, aromatic);6.70-6.50(1H, m, CH=C); 4.94(2H, t, N-CH:);4.20-4.05(2H, m, N-CH:); 3.80-3.60(2H, m, N-CH_2);3.25-3.00(4H, m, 2 x CH:): 2.72(3H, s, N-CH_3) p.p.m.

Example 2:

2,3-Dihydro-9(1-Methyl-1,2,5,6-Tetrahydro-4-Pyridyl) 1-4-Pyrazolo-(1,2-a)-Indazolium Bromide (Compound R77).

The title compound was prepared as described in Example 1 except that compound C was prepared as follows from (2-amino-4-chlorophenyl)-4-pyridyl-methanone:

(2-Amino-4-chlorophenyl)-4- pyridyl-methanone (120mg; 0.52 mmpl), prepared according to the literature method, was dissolved in ethanol (15ml) at ambient temperature under nitrogen. Palladium 10% on carbon (70mg) was added and the mixture refluxed

for thirty minutes. After cooling, the catalyst was removed by filtration through celite and the solvent was removed by evaporation at reduced pressure. The residue was taken up in ethyl ethanoate (80ml), washed with water (15ml), dried over magnesium sulphate and filtered. Evaporation of the solvent gave the impure product which was purified by flash chromatography on silica to give the pure product (80mg, 78%), identical to that previously prepared (vide supra).

Example 3:

2,3-Dihydro-9(1-Methyl-1,2,5,6-Tetrahydro-4-Pyridyl) 1-4-Pyrazolo-(1,2-a)-Indazolium Bromide (Compound R77).

The title compound was prepared as described in Example 1 except that compound E was prepared from 2-aminophenyl-4-pyridyl-methanone using sodium bisulphite:

2-Aminophenyl-4-pyridyl-methanone (3.1g; 16 mmol) was dissolved in 10M aqueous hydrochloric acid (35ml) at 0°C with stirring. Sodium nitrite (1.0g) in water (7.5ml) was added dropwise over five minutes. After stirring for a further hour sodium bisulphite (10g) was added in portions. After stirring for thirty minutes at 0°C and one hour at ambient temperature, the reaction was extracted with ethyl ethanoate (3 x 400ml), dried, filtered and the solvent removed under reduced pressure. Flash silica chromatography provide slightly impure indazole (630mg; 21%). Further silica chromatography provided pure material (480mg; 16%) identical to that previous prepared (vide supra).

Example 4:

2,3-Dihydro-9(1-Methyl-1,2,5,6-Tetrahydro-4-Pyridyl) 1-4-Pyrazolo-(1,2-a)-Indazolium Bromide (Compound R77).

The title compound was prepared as described in Example 1 except that compound E was prepared from 2-aminophenyl-4-pyridyl-methanone using tin dichloride:

2-Aminophenyl-4-pyridyl-methanone (4.9g; 25 mmol) was

dissolved in 10M aqueous hydrochloric acid (30ml) at 0°C under a nitrogen atmosphere. Sodium nitrite (2.0g) dissolved in water (8.5ml) was added dropwise over fifteen minutes. After stirring for a further hour, tin dichloride dihydrate (11g) in water (100ml) was added dropwise over fifteen minutes. After stirring for one hour at ambient temperature, the reaction mixture was cooled to 0°C and saturated aqueous sodium carbonate was added dropwise until the mixture was basic. This was then evaporated to dryness, extracted into methanol, filtered and the solvent evaporated. Flash silica chromatography provided the product (3.8g; 79%), which was identical to that previously prepared (vide supra).

Example 5:

2,3-Dihydro-9(1-Methyl-1,2,5,6-Tetrahydro-4-Pyridyl) 1-4-Pyrazolo-(1,2-a)-Indazolium Bromide (Compound R77).

The title compound was prepared as described in Example 1 except that compound E was prepared from (2-amino-5-chloro-phenyl)-4-pyridyl-methanone as follows:

(2-Amino-5-chlorophenyl)-4-pyridyl-methanone (1.16g; 5.05 mmol) was dissolved in 10M aqueous hydrochloric acid (5ml) at 0°C with stirring and under a nitrogen atmosphere. Sodium nitrite (380mg) dissolved in water (1.5ml) was added dropwise over a period of about five minutes. After a further thirty minutes, sodium bisulphite (3.8g) dissolved in water (20ml) was added dropwise over ten minutes. The reaction mixture was stirred for thirty minutes at 0°C and thirty minutes at ambient temperature. The solution was made alkaline with 2M aqueous sodium hydroxide and the extracted with ethyl ethanoate (3 x 100ml). The dark red coloured extract became golden brown coloured when dried over a mixture of potassium carbonate and magnesium sulphate. After filtering and evaporating the solvent, the intermediate was obtained using radial chromatography on silica as a yellow oil, 5-chloro-3-(4-pyridyl)-indazole (450mg; 39%).

i.r. (N-H) 2500-3300cm^{-1}

^{1}H n.m.r. 8.71 (2H, complex d, pyridyl); 7.81 (2H, complex d, pyridyl); 7.99 (1H, dd, C(5)-H) 7.42 (2H, m, C(7)-H and C (8)-H) p.p.m.

Repetition provided a larger quantity of this intermediate, a portion of which (960mg; 4.2 mmol) was dissolved in ethanol (50ml) and hydrazine hydrate (12.5ml). After adding 10% palladium-carbon (500mg) under nitrogen, the reaction mixture was refluxed for ten minutes. The catalyst was removed by filtration then the volatiles were removed under reduced pressure. The residue was taken up in ethyl ethanoate (250ml), washed with water (50ml), dried over magnesium sulphate and filtered. Radial silica chromatography of the material, obtained by evaporation, provided pure product (550mg; 67%) as a white solid, identical to that previously prepared (vide supra).

Example 6:

2,3-Dihydro-9(1-metyyl)-4-piperidyl)-1-4-pyrazolo-(1,2a)-indazolium bromide (compound R78)

A. 3-(1-Methyl-1,2,5,6-tetrahydro-4-pyridyl)-2-methylindole.

2-Methylindole (50g; 0.38 mol) dissolved in glacial ethanoic acid (1l) was stirred at 70°C (oil bath) and 2N aqueous phosphoric acid (250ml) and 1-methyl-4-piperidone (93.8ml; 0.76 mol) were added. Stirring was continued at this temperature for two hours, after which the reaction was cooled to 0°C (ice:water) and a mixture of 0.88 ammonia:ice was added, with vigorous stirring, until no more brown precipitate formed. This precipitate was filtered off, lightly washed with water until neutral, dried, filtered and the solvent evaporated to give a brown solid (70.2g; 81%). Recrystallisation of a small sample gave the pure product in the form of off-white needles, from diethyl ether and petroleum ether.

m.p. 138-140°C.
i.r. 3472 (NH); 2788 (N-CH_3) cm^{-1}.
^1H n.m.r. 1.46 (1H, b, NH); 2.27-3.23 (4H, m, aromatic); 4.29 (1H, b, CH); 6.59-7.82 (6H, m, CH_2); 7.57 (3H, s, N-CH_3); 7.72 (3H, s, indole CH_3) p.p.m.
m.s. M^+ 226.

B. 3-(4-(1-Methyl)-piperidyl)-2-methylindole.

3-(1-Methyl-1,2,5,6-tetrahydro-4-pyridyl)-2-methylindole (68g; 0.30 mol) was reduced in portions. Vigorously stirred portions (4.0g) of starting material in a mixture of ethanol (160ml), water (200ml) and 10M aqueous hydrochloric acid (40ml) were hydrogenated over 5% palladium on carbon (0.4g; 10% by weight) at room temperature until the theoretical volume of hydrogen was consumed (400ml). The reaction mixtures were filtered through celite, neutralised with 10M aqueous sodium hydroxide and, under reduced pressure, evaporated almost to dryness and extracted with ethyl ethanoate. The extract was dried, filtered and evaporated to give a brown solid (65.2g; 95%). Recrystallisation gave the pure product in the form of yellow crystals, from diethyl ether and petroleum ether.

m.p. 166-168°C.
i.r. 3473 (NH); 2790 (N-CH_3) cm^{-1}
^1H n.m.r. 1.91 (1H, b, NH); 2.15-3.22 (4H, m, aromatic); 6.76-8.52 (9H, m, CH/CH_2); 7.66 (6H, s, 2 x CH_3) p.p.m.
^{13}C n.m.r. ($CDCl_3$): 135.3(s); 129.9(s); 127.5(s); 120.5(d); 119.1 (d); 118.7(d); 115.1 (s); 110.2(d); 56.9(t); 46.7(q); 34.0(d); 32.0(t) p.p.m.

C. (2-Ethanamidophenyl)-(4-(1-methyl)-piperidyl)-methanone.

Sodium periodate (47g; 0.22 mol) in water (600ml) was added in aliquots to a stirred solution of 3-(4-(1-methyl)-piperidyl)-2-methylindole (20g; 0.088 mol) in methanol (400ml) at room temperature and the white precipitate,

which formed throughout the reaction, was periodically filtered off. After two days the solution was filtered and, under reduced pressure, evaporated almost to dryness. The reaction mixture was extracted with trichloromethane. The extract was dried, filtered and evaporated to give a brown oil (13.7g, 60%). Silica chromatography gave the pure product in the form of a yellow oil.

i.r. 3253 (NH); 2793 ($N-CH_3$); 1690 ($NHCOCH_3$); 1648 (C=O) $cm.^{-1}$

^1H n.m.r. 1.12-1.34 (1H, m, aromatic); 1.95-3.03 (3H, m, aromatic); 6.51-8.40 (9H, m, CH/CH_2); 7.67(3H, s, $N-CH_3$); 7.77(3H, s, CH_3) p.p.m.

^{13}C n.m.r. (CD_3OD): 208.1 (s); 171.6(s)1 141.0(s); 135.2(d); 131.7(d); 124.5(d); 124.2(s); 122.8(d); 55.7(t); 46.1 (q); 44.9(d); 29.5(t); 24.9(q) p.p.m.

D. (2-Aminophenyl)-(4-(1-methyl)-piperidyl)-methanone

2-(Ethanamidophenyl)-(4-(1-methyl)-piperndyl)-methanone was converted into the title compound by following a standard acid hydrolysis procedure.

E. (2-Azidophenyl)-(4-(1-methyl)-piperidyl)-methanone.

(2-Aminophenyl)-(4-(1-methyl)-piperidyl)-methanone (16.4g; 75 mmol) was dissolved with a little warming in 10M aqueous hydrochloric acid (200ml) and stirred at 0°C (ice/water). Sodium nitrite (6.75g; 0.98 mol) in water (50ml) was added dropwise. After thirty minutes sodium azide (12.7g; 0.196 mol) in water (100ml) was also added dropwise, and stirring was continued for a further thirty minutes. The reaction was neutralised by pouring it slowly onto a vigorously stirred mixture of ethyl ethanoate and 2M aqueous sodium hydroxide. The ethyl ethanoate was separated and, after further extracting the aqueous portion with

ethyl ethanoate, the organic portions were combined, washed with water until neutral, dried, filtered and evaporated to give a brown oil (13.2g, 72%). Silica chromatography of a small sample gave the pure product in the form of a yellow oil.

i.r. 2791 ($N-CH_3$); 2127 (N_3); 1683 ($C=O$) cm^{-1}

^1H n.m.r. 2.32-3.05 (4H, m, aromatic); 6.54-8.35 (9H, m, CH/CH_2); 7.71 (3H, s, CH_3) p.p.m.

F. 3-(4(1-Methyl)piperidyl)-indazole.

(From (2-azidophenyl)-(4-(1-methyl)-piperidyl)-methanone.)

(2-Azido phenyl)-(4-(1-methyl)-piperidyl)-methanone (16.5g; 68 mmol) in ethanol (400ml) was refluxed with hydrazine hydrate (65.5ml; 1.35 mol) and glacial ethanoic acid (10ml) for one day. The reaction was neutralised with glacial ethanoic acid, and after adding water, evaporating off most of the ethanol under reduced pressure and slight basification of the remaining solution, extraction with trichloromethane, drying, filtering and evaporating gave a brown solid (6.0g; 41%). Silica chromatography of a small sample gave the pure product as a yellow solid.

m.p. 159-161°C.

i.r. 3472 (NH); 2792 ($N-CH_3$) cm^{-1}

^1H n.m.r. 8.01-6.90 (4H, m, aromatic); 3.44-1.87 (9H, m, CH/CH_2); 2.37 (3H, s, CH_3) p.p.m.

m.s. M±215; M±-CH_3 200.

G. 2,3-Dihydro-9(1-methyl-4-piperidyl)-1-4-pyrazolo-1,2a)-indazolium bromide (Compound R78).

3-(4-(1-Methyl)piperidyl)-indazole is converted into the title compound (R78) by a procedure similar to that described in Example 1 H.

Example 7:

2,3-Dihydro-9(1-methyl-4-piperidyl)-1-4-pyrazolo-1,2a)-indazolium bromide (Compound R78).

The title compound was prepared as described in Example 6

except that compound F was prepared from 3-(1-Methyl-1,2,5,6-tetrahydro-pyrid-4-yl)-indazole as follows:

3-(1-Methyl-1,2,5,6-tetrahydro-pyrid-4yl)-indazole (1.0; 4.6 mmol) was dissolved in tetrahydrofuran (20ml) at 0°C (ice/water) followed by the addition of trimethylamine N-oxide dihydrate (1.4g; 13 mmol). The reaction mixture was refluxed for five hours, then the solvent was evaporated and the residue was dissolved in diglyme (15ml). After refluxing for one hour, the solvent was evaporated to give a yellow oil (0.4g, 45%). Purification by silica chromatography gave the product as a yellow solid, identical to the product prepared previously (vide supra).

Example 8:

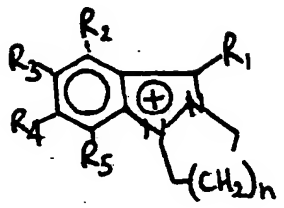
2,3-Dihydro-9(1-methyl-4-piperidyl)-1-4-pyrazolo-1,2a)-indazolium bromide (Compound R78).

The title compound was prepared as described in Example 6 except that compound F was prepared from (2-aminophenyl)-(4-(1-methyl)-piperidyl)-methanone as follows:

(2-Aminophenyl)-(4-(1-methyl)-piperidyl)-methanone (3.1g, 14.2 mmol) was dissolved in 10M aqueous hydrochloric acid at 0°C with stirring. After fifteen minutes, sodium nitrite (1.30g) in water (5.5ml) was added dropwise over a period of fifteen minutes. After stirring for one hour, tin dichloride trihydrate (7.5g) in water (60ml) was added dropwise over fifteen minutes. The reaction mixture was then allowed to reach ambient temperature. After two hours, the reaction was made basic with saturated aqueous sodium carbonate and then extracted with trichloromethane. After drying and filtering, the solvent was evaporated to give 3-(1-methyl-4-piperidyl)-indazole (1.2g). Evaporation of the aqueous phase, extraction into methanol and flash chromatography on silica provided more of the indazole (1.0g: total 2.2g; 72%). The physical properties of the compound prepared in this fashion were identical to those of the material obtained by the alternative methods, (vide supra).

CLAIMS

1. A compound of formula II or a pharmaceutically acceptable acid addition salt thereof:

II  X^-

in which formula R_1 represents a six membered heterocyclic ring A comprising one nitrogen atom and bound to the indazole ring system by carbon, the ring A being optionally substituted by one or more C_1-C_6 alkyl groups;

R_2 represent hydrogen, hydroxy, C_1-C_6 alkyl or C_1-C_6 alkoxy,

R_3 represents hydrogen, hydroxy, halogen, a C_1-C_6 alkyl or alkoxy group, or a group of formula $-NO_2$, -CN,$-CONH_2$, or -CONHR (R representing a C_1-C_3 alkyl group);

R_4, which may differ from R_3, represents: hydrogen, hydroxy, halogen, a C_1-C_6 alkyl or alkoxy group, or a group of formula $-NO_2$, -CN,$-CONH_2$, or -CONHR (R representing a C_1-C_3 alkyl group);

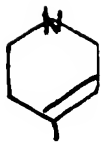
R_5 represents hydrogen or halogen,

X^- represents an anionic moiety the nature of which is such that the compound of formula II is pharmaceutically acceptable and

n is 1 or 2.

2. A compound according to Claim 1, in which the nitrogen atom of ring A is spaced by three carbon atoms from the carbon of the indazole ring system on which ring A is carried.

3. A compound according to any preceding Claim, in which R_1 has the formula:



4. A compound according to Claim 3, in which the nitrogen of group R_1 carries a C_1-C_6 alkyl group.

5. A compound according to any preceding claim, in which R_2 represents hydrogen, hydroxy, C_1-C_3 alkyl or alkoxy.

6. A compound according to any preceding claim, in which X^- represents halide.

7. A compound according to any preceding claim, in which R_3 represents hydrogen, hydroxy, C_1-C_3 alkyl or alkoxy or halogen.

8. A compound according to any preceding claim, in which R_4 represents hydrogen, hydroxy, C_1-C_3 alkyl or alkoxy or halogen.

9. A compound according to any preceding claim, in which n is one.

10. A compound according to any preceding claim, in which R_4 and R_5 represent hydrogen.

11. A compound according to any preceding claim, in which R_2 represents hydrogen or C_1-C_6 alkoxy.

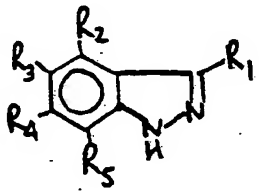
12. A compound which is: (i) 2,3-Dihydro-9(1-methyl-1,2,5,6 tetrahydro-4-pyridyl)-1-4-pyrazolo(1,2-a)indazolium bromide; (ii) 2,3-dihydro-9-(1-methyl)-4-pyridyl)-1-4-pyrazolo-(1,2a)-indazolium bromide; (iii) 2,3-dihydro-9-(1-methyl)-4-piperidyl)-1-4-pyrazolo-(1,2a)-indazolium bromide; (iv) 7-methyl-2,3-dihydro-9(1-methyl-1,2,5,6 tetrahydropyridyl)-1-4 pyrazolo-(1,2-a)-indazolium bromide or (v) 7-methyl-2,3-dihydro-9(1-ethyl-1,2,5,6 tetrahydropyridyl)-1-4-pyrazolo(1,2-a) indazolium bromide or an acid addition salt of such a compound.

13. A compound according to any preceding claim for use in therapy.

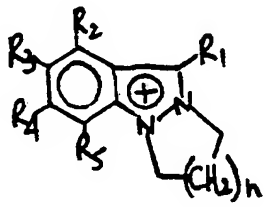
14. A method for the treatment or prophylaxis of asthma in which an asthmatic subject is treated with a compound according to any of Claims 1 to 12 in an amount effective to dilate the bronchi of the subject.

15. A composition for the treatment or prophylaxis of asthma which comprises a compound according to any of Claims 1 to 12 together with an inert carrier or diluent.

16. A process for the production of a compound II or a pharmaceutically acceptable acid addition salt thereof comprises treating an indazole of formula III or an acid addition salt thereof,

III 

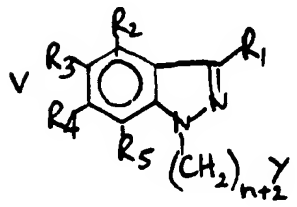
with a substituted alkane of formula $Y-(CH_2)_{n+2}-Z$ wherein Y and Z which may be identical or different, represent moieties capable of existence as anions in the presence of a reducing agent such as a hydride e.g. an alkali metal hydride whereby a compound of formula IV is produced the counterion Y^- of which is, when necessary, subsequently replaced by a counterion X^-.

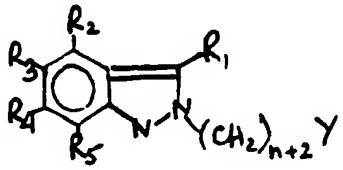
IV  Y^-

17. An indazole of formula III or an acid addition salt thereof hereinbefore described.

18. An intermediate of formula IV or an acid addition salt thereof hereinbefore described.

19. An intermediate of formula V or VI or an acid addition salt thereof hereinbefore described.





INTERNATIONAL SEARCH REPORT

International Application No PCT/GB 89/00517

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC[4] C 07 D 487/04, A 61 K 31/435, C 07 D 401/04, // (C 07 D 487/04, IPC[4]: 231:00, 231:00), (C 07 D 487/04, 237:00, 231:00)

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
IPC[4]	C 07 D 487/00, A 61 K 31/00, C 07 D 401/00

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category *	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
X	DE, A, 1266763 (KALLE) 25 April 1968 see column 7, compound 14	17
X	US, A, 3678062 (AMERICAN CYANAMID) 18 July 1972 see example 1	17
X	Helvetica Chimica Acta, volume 65, fasc. 3, no. 78, 1982, Schweizerische Chemische Gesellschaft, (Basel, CH), K.-H. Pfoertner et al.: "Herstellung der 1H-Indazole durch Photolyse von 2-Aminophenylketon-O-(äthoxycarbonyl) oximen und von 3,1,4 - Benzoxadiazepin-2(1H)-onen", pages 798-806 see page 806, compound 2c	17
X	EP, A, 0135781 (HOECHST-ROUSSEL) 3 April 1985 see claim 1	17

./.

* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
7th August 1989	05.09.89
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	P.C.G. VAN DER PUTTEN

International Application No. PCT/GB 89/00517

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

A	EP, A, 0023633 (CHUGAI) 11 February 1981 see claim 1 and pages 7,8, experiment ---	1,15

V. ☒ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. ☒ Claim numbers 1-4, because they relate to subject matter not required to be searched by this Authority, namely:

See Rule 39 i(iv) PCT: Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.

2. ☐ Claim numbers ....., because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claim numbers ....., because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. ☐ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this international application as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

☐ The additional search fees were accompanied by applicant's protest.

☐ No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. GB 8900517 SA 28650

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 29/08/89
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
DE-A- 1266763		None	
US-A- 3678062	18-07-72	None	
EP-A- 0135781	03-04-85	AU-B- 575846	11-08-88
		AU-A- 3225084	28-02-85
		JP-A- 60100573	04-06-85
		US-A- 4710573	01-12-87
EP-A- 0023633	11-02-81	JP-A- 56015287	14-02-81
		CA-A- 1151176	02-08-83
		US-A- 4409234	11-10-83